CHAPTER 13

Pharmacological Approaches to Cognitive Deficits Associated with PTSD

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There are a number of cognitive deficits that appear to be associated with posttraumatic stress disorder (PTSD). Among adults, the focus has primarily been on memory function and information processing based in part on reports of reduced hippocampal volume among PTSD patients (Bremner, Randall, et al., 1997; Bremner, Vythilingam, et al., 2003). Among children, there has been concern that trauma/PTSD-related deficits in intelligence may be related, developmentally, to reduced intracranial and corpus callosum volumes (De Bellis et al., 2002).

The presumed circuitry underlying such abnormalities focuses on excessive activation of the amygdala by stimuli perceived to be threatening. Such activation produces outputs to a number of brain areas that mediate memory consolidation of emotional events and spatial learning (hippocampus), memory of emotional events and choice behaviors (orbitofrontal cortex), autonomic and fear reactions (locus coeruleus, thalamus, and hypothalamus), and instrumental approach or avoidance behavior (dorsal and ventral striatum) (Davis & Whalen, 2001). In PTSD, the normal checks and balances on amygdala activation have been impaired so that the restraining influence of the medial prefrontal cortex (PFC), especially the anterior cingulate gyrus and orbitofrontal cortex, are severely disrupted (Charney, 2004; Vermetten & Bremner, 2002). Disinhibition of the amygdala produces a vicious spiral of recurrent fear conditioning in which am-

biguous stimuli are more likely to be appraised as threatening; mechanisms for extinguishing such responses are nullified; and key limbic nuclei are sensitized thereby lowering the threshold for fearful reactivity (Charney, Deutch, Krystal, Southwick, & Davis, 1993, 2004; Friedman, 1994; Southwick, Rasmusson, Barron, & Arnsten, Chapter 2, this volume).

The pharmacological challenge, therefore, is to identify where and how to intervene in order to rein in the amygdala and the cortical and subcortical effects it has set in motion. Although many neurobiological systems are altered among individuals with PTSD, we must first consider the adrenergic, hypothalamic–pituitary–adrenal (HPA), and glutamatergic systems because they appear to be most important with regard to cognitive deficits. Serotonergic and dopaminergic mechanisms will also be discussed.

A thorough review of PTSD-related neurochemical alterations associated with cognitive abnormalities is beyond the scope of this chapter and can be found elsewhere (Charney, 2004; Southwick et al., Chapter 2, this volume; Vermetten & Bremner, 2002). A brief summary of major findings is shown in Table 13.1.

This chapter is concerned with pharmacological interventions to reverse such alterations. It should be stated at the outset, that, with a few exceptions, I can offer little more than theoretically driven speculations rather than a review of empirical findings. This is because most research with pharmacological agents has focused on reduction of PTSD symptoms rather than amelioration of cognitive impairment. Furthermore, the lion's share of such investigations concern serotonergic agents rather than other classes of medications. Table 13.1 summarizes all the findings that will be reviewed. It specifies the mechanism of action for each pharmacological agent as well as the cognitive and clinical effects for each medication under consideration.

THE ADRENERGIC SYSTEM AND ANTIADRENERGIC AGENTS

Norepinephrine

Animal research indicates that central noradrenergic neurons play an important role in determining alertness, vigilence, orienting to novel stimuli and selective attention. All three principle adrenergic receptor systems are involved in the fear conditioning circuitry described previously. (A more thorough review is provided by Southwick, Rasmnsson, Barron, & Arnsten, Chapter 2, this volume). *Beta-adrenergic receptors* mediate the enhancement of emotional memory by the amygdala (Cahill & McGaugh, 1996). Such enhancement may be related to the intrusive recollections, dissociative flashbacks and psychological/physiological reactivity provoked by exposure to traumatic stimuli that are usually seen among individuals

TABLE 13.1. Pharmacological Actions Affecting Cognition in PTSD

Pharmacological category	Specific medication	Mechanism of action	Effect on stress/fear response	Effects on cognition	Clinical findings
Adrenergic system	Propranolol	Beta-receptor antagonist.	All antiadrenergic agents: • Reduce amygdala activation. • Enhance PFC function. • Inhibit locus coeruleus activation.	All antiadrenergic agents: • Reduce consolidation of emotional memories. • Enhance working memory. • Reduce dissociative symptoms.	• All reduce PTSD symptoms (mostly reexperiencing and hyperarousal). • Propranolol reduces stress-related enhancement of emotional memories. • Prazosin reduces nightmares. • Clonidine/guanfacine enhance PFC working memory function and reduce dissociation.
	Prazosin	Alpha$_1$-receptor antagonist.			
	Clonidine/ guanfacine	Alpha$_2$-receptor antagonist.			
	Theoretical	NPY enhancer.	• Antagonizes both adrenergic and CRF activation of fear/stress response. • Suppresses adrenergic and HPA responses to stress.	• Untested. • Theoretically, should enhance cognition and working memory. • Theoretically, should reduce consolidation of emotional memories and dissociation.	• Hypothetical medication.
HPA system	Antalarmin[a]	CRF antagonist.	• Suppresses adrenergic and HPA responses to stress. • Reduces CRF release. • Reduces locus coeruleus activation. • Reduces ACTH secretion with secondary glucocorticoid elevation.	• Reduces stress-induced fearful behavior. • Should enhance cognition and working memory. • Should reduce consolidation of fearful memories and dissociation.	• Safe CRF antagonists, suitable for clinical studies, are not available.

	Hydrocortisone, other glucocorticiods.	Rectify hypocortisolism and downregulate GC receptors.	• Reduces increased HPA activation thereby reducing potentiation of excessive adrenergic activity.	• Untested.	• Although HPA activation appears to be associated with PTSD, findings regarding cortisol levels and GC supersensitivity are inconsistent, therefore scenarios with medications that both increase and decrease glucocorticoid levels and GC receptor activation are presented.
	Ketoconazole	Blocks cortisol synthesis.			
	Mifepristone (RU-486)	GC receptor antagonist.	• Reduces cortisol's neuroroxic enhancement of glutamate and calcium influx into neurons.		
Glumatergic system	Cycloserine	Partial NMDA receptor agonist.	• Enhances learning, extinction, memory function, and neurogenesis.	• Improvement in Wisconsin Card Sort persevcrarive error scores and near significant improvement in delayed recall on Auditory Verbal Learning Test.	• RCT on augmentation treatment showed cognitive benefits as well as reduction in PTSD severity and general anxiety.
GABAergic agents	Benzodiazepines	$GABA_A$ rcceptor agonist.	• Suppress stress-induced amygdala activation by inhibition of NMDA receptors.	• Untested. (predict enhanced cognition by anragonizing amygdala activarion if sedation and cognitive blunting can be prevented).	• Clinical trials indicate no specific efficacy against core PTSD symptoms.
	Baclofen	$GABA_B$ receptor agonist.	• Unclear. • Might reduce stress-induced adrenergic/HPA activation. • Has been effective clinically in mood and anxiety disorders.	• Untested.	• One small open trial showing improvement in overall PTSD symptom severity.
Anriconvulsants/ antikindling agents	Carbamazepine	• AMPA antagonist. • Elevates GABA. • Blocks sodium channels.	• Blocks sensitizarion/ kindling. • Suppresses adrenergic arousal.	• Untested.	• Open trials show reduced PTSD severity, arousal, impulse control, aggression and violent behavior.

(continued)

TABLE 13.1. Pharmacological Actions Affecting Cognition in PTSD

Pharmacological category	Specific medication	Mechanism of action	Effect on stress/fear response	Effects on cognition	Clinical findings
	Valproate	• Increases brain GABA levels. • Enhances GABA receptor sensitivity.	• Blocks sensitization/kindling. • May suppress NMDA receptors.	• Untested.	• Open trials and case reports indicate clinical efficacy in PTSD.
	Lamotrigine	• Inhibits glutamate release. • Blocks voltage-dependent sodium and calcium channels.	• Blocks sensitization/kindling. • Blocks NMDA activation of amygdala.	• Inhibits dissociatve symptoms caused by ketamine and phencyclidine.	• Small, randomized trial suggests favorable effect in PTSD.
	Topirimate	• Suppresses glutamate function. • Enhances GABA activity.	• Blocks sensitization/kindling. • Blocks NMDA amygdala activarion.	• Untested.	• Open trial showed suppression of PTSD reexperiencing and dissociative symptoms.
	Gabapentin	• Increases GABA turnover.	• Blocks sensirization/kindling.	• Untested.	• Case reports and chart reviews suggest effectiveness in PTSD.
	Tiagabine	• Increases GABA levels by inhibiting glial uptake.	• Blocks sensitization/kindling.	• Untested.	• Positive case reports.
	Vigabatrin	• Increases GABA by inhibiting GABA transaminase.	• Blocks sensitization/kindling. • Blocks startle response.	• Untested.	• Case reports showing reduction of insomnia, anxiety, and startle response in PTSD patients.
Selective serotonin reuptake inhibitors (SSRIs)	Paroxetine	• SSRI.	• 5-HT-$_{1A}$ neurons potentiate GABA antagonism of amygdala NMDA activity. • Promotes neurogenesis in hippocampus.	• Increased hippocampal volume after 9-12 months of treatment associated with cognitive improvement in: logical, figural, verbal, and visual memory.	• FDA approval for PTSD based on three randomized clinical trials. • Broad spectrum of action against all three PTSD symptom clusters.

	Sertraline	SSRI.	• See paroxetine.	• Untested.	• FDA approval for PTSD based on two randomized clinical trials. • Broad spectrum of action.
	Fluoxetine	SSRI.	• See paroxetine.	• Untested.	• Successful randomized clinical trials in PTSD.
	Fluvoxamine	SSRI.	• See paroxetine.	• Untested.	• Successful open-label trials.
	Citalopram	SSRI.	• See paroxetine.	• Untested.	• Successful open-label trial.
Other serotonergic antidepressants	Nefazodone[b] Trazodone	SSRI plus post-synaptic 5-HT_2 blockade.	• In addition to potentiation of 5-HT_{1A} action, blockade of 5-HT_2 receptors is anxiolytic. • Promotes neurogenesis.	• Untested.	• Randomized and open-label trials suggest nefazadone is as effective as sertraline. • Trazodone has limited efficacy. • Nefazodone is no longer available in the USA because of liver toxicity.
Tricyclic antidepressants (TCAs)	Imipramine Amitriptyline Desipramine	Blocks presynaptic reuptake of norepinephrine and serotonin.	• Enhance serotonergic actions at 5HT1A receptors. • Reduce adrenergic actions by downregulation of postsynaptic beta receptors. • Promote neurogenesis.	• Untested.	• Successful randomized trials for PTSD patients with imipramine and amitriptyline but not desipramine.
Monoamine oxidase inhibitors (MAOIs)	Phenelzine	Blocks enzymatic (MAO) degradation of norepinephrine, serotonin (and dopamine).	• Enhances serotonergic action at 5-HT_{1A} receptors. • Downregulates postsynaptic beta receptors (and reduces locus coeruleus activity). • Promotes neurogenesis.	• Untested.	• Mixed results with phenelzine. A positive randomized trial, an inconclusive cross-over trial and mixed findings in open-label trials. • One positive open-label trial with moclobemide.
	Moclobemide	Selective MAO-A inhibitor.			

(*continued*)

TABLE 13.1. Pharmacological Actions Affecting Cognition in PTSD

Pharmacological category	Specific medication	Mechanism of action	Effect on stress/fear response	Effects on cognition	Clinical findings
Other antidepressants	Mirtazepine	Blocks postsynaptic 5-HT_2 and 5-HT_3 receptors.	• Anxiolytic 5-HT_2/5-HT_3 blockade. • Reduces adrenergic activity. • All three antidpressants promote neurogenesis. • Potentiates 5-HT and reduces adrenergic activity. • Reduces adrenergic and dopaminergic activity.	• Untested.	• Mirtazepine reduced PTSD symptom severity in one randomized and one open-label trial as well in case reports. • Favorable open trials with venlafaxine and bupropion.
	Venlafaxine	Agonist action at presynaptic adrenergic alpha$_2$ receptors. Blocks presynaptic reuptake of both serotonin and norepinephrine.			
	Bupropion	Blocks presynaptic reuptake of norepinephrine and dopamine.			
Atypical antipsychotic agents	Risperidone Quetiapine Olanzapine	Dopamine (D_2) and serotonin (5-HT_2) blockade.	• Promotes enhanced PFC restraint of amygdala, reduces hyperarousal/ hypervigilence and blocks anxiogenic 5-HT_2 receptor actions.	• Untested (predict enhancement of PFC working memory and reduction in consolidation of emotional memories).	• *Risperidone* Augmentation reduced PTSD symptom severity, dissociative flashbacks and aggressive behavior—one RCT, one open trial and several case reports. • *Quetiapine* Augmentation was beneficial in reducing PTSD severity in SSRI non responders—one open trial, a retrospective chart review and case reports. • *Olanzapine* Augmentation reduced PTSD severity in SSRI non responders.

Note. ACTH, corticotropin; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxyazoleproprionic acid; CRF, corticotropin-releasing factor; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GC, glucocorticoid; 5-HT, serotonin; MAO, monoamine oxidase; NMDA, *N*-methyl-D-aspartate; NPY, neuropeptide Y; PFC, prefrontal cortex; RCT, randomized clinical trial; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Experimental medication.

[b]Withdrawn from U.S. market because of liver toxicity.

with PTSD. *Alpha$_1$-adrenergic receptors* also promote this process by facilitating the impact of beta-adrenergic enhancement of memory. This postsynaptic noradrenergic input to both beta and alpha$_1$ receptors promotes activation of the amygdala. Because the amygdala's projections to the locus coeruleus generate additional adrenergic input, it can be seen how this process can escalate and result in an upward spiral of adrenergic stimulation.

Alpha$_2$-adrenergic receptors, which provide presynaptic inhibition of amygdala catecholamine release, suppress fear conditioning and reduce consolidation of emotional memories (Davies et al., 2004). They may also play a role in dissociation since the alpha$_2$ antagonist, yohimbine (which disinhibits adrenergic activity), provoked dissociative flashbacks among Vietnam veterans with PTSD (Southwick et al., 1997, 1999). Thus, from the perspective of the amygdala, alone, agents that antagonize alpha$_1$- and beta-adrenergic receptors or enhance alpha$_2$-adrenergic activity might be expected to improve cognitive function.

Unlike the amygdala, which thrives in a climate of elevated adrenergic stimulation, the opposite is true for the PFC. High levels of catecholamines impair PFC function. In addition to modulating amygdala activity, the PFC mediates working memory. Thus, increasing adrenergic stimulation not only reduces the PFC's capacity to inhibit amygdala hyperactivity, but also impairs its cognitive role in working memory and maintenance of attention (Arnsten, 2000). Both alpha$_1$ and beta-receptor activation appear responsible for nullifying PFC activity during uncontrollable stress and these effects can be prevented with alpha$_1$-adrenergic antagonists such as prazosin (Arnsten & Jentsch, 1997) as well as with the beta-adrenergic antagonist, propranolol (Li & Mei, 1994).

To summarize, the therapeutic goal of targeting the adrenergic system is to inhibit excessive alpha$_1$ and beta-receptor activation and to augment the inhibitory influence of alpha$_2$-adrenergic receptors. The result of such treatment would be expected to reduce amygdala activation, enhance PFC function, and inhibit stimulation of the locus coeruleus and its secondary activation of other cortical and subcortical structures. Cognitive benefits should include reduced consolidation of fearful memories, enhancement of PFC working memory capability, and prevention of fragmented information processing, manifested as dissociative symptoms.

There are little empirical data to guide us. Cahill and McGaugh, (1996) have shown that the beta-adrenergic antagonist *propranolol* reduced enhancement of emotional memories among human volunteers. In small studies with clinical populations, propranolol has had beneficial effects on PTSD symptoms (including intrusive recollections and reactivity to traumatic stimuli) (Famularo, Kinscherff, & Fenton, 1988; Kolb, Burris, & Griffiths, 1984; Pitman et al., 2002; Taylor & Cahill, 2002; Vaiva et al., 2003). It should be noted that these were all small studies and that formal

tests of cognitive function were not performed in any of these investigations.

Recent research with the alpha$_1$ antagonist, *prazosin*, has indicated that PTSD nightmares and other symptoms are reduced by treatment (Peskind, Bonner, Hoff, & Raskind, 2003; Raskind, Peskind, Kanter, Petrie, Radont, Thompson, et al., 2003). Since prazosin would be expected to improve PFC and reduce amygdala activation, it is expected that this agent would also improve cognition among PTSD patients.

Alpha$_2$-adrenergic agonists such as *clonidine* and *guanfacine* would also be expected to improve PFC cognitive function in addition to directly reducing amygdala activity. Animal research has shown that alpha$_2$ agonists enhance PFC working memory function (Franowicz et al., 2002; Mao, Arnsten, & Li, 1999). Again, however, the sparse, but generally favorable, clinical literature on the clinical efficacy of these agents in PTSD (Kinzie & Friedman, 2004; Kolb et al., 1984) has not included formal assessment of cognitive function.

Neuropeptide Y

Neuropeptide Y (NPY) is an amino acid neurotransmitter, colocalized in noradrenergic neurons, that inhibits the release of both norepinephrine and corticotropin-releasing factor (CRF, see later in the chapter). By virtue of its endogenous antiadrenergic actions, NPY would be expected to produce the antistress/anxiolytic benefits postulated above for antiadrenergic agents and, thereby improve cognitive function. Indirect evidence for this assertion has been obtained in studies of military personnel exposed to extreme stress in which there was an inverse relationship between NPY release and stress-induced performance decrements due to dissociation (Morgan et al., 2000, 2001). Clinically, it has been shown that, in comparison with healthy controls, PTSD patients exhibit both reduced baseline NPY levels and a blunted release of NPY in response to yohimbine stimulation (Rasmusson et al., 2000). Based on such findings, I have previously suggested that medications that enhance NPY function might ameliorate acute stress reactions, PTSD, and other stress-induced problems (Friedman, 2002). No pharmacological agents of this nature are currently available.

CORTICOTROPIN-RELEASING FACTOR AND THE HYPOTHALAMIC-PITUITARY-ADRENAL SYSTEM

Corticotropin-Releasing Factor

Corticotropin-releasing factor (CRF) has a dual role in the human stress response. As a neurotransmitter it promotes release of norepinephrine from the locus coeruleus, thereby enhancing amygdala and reducing PFC activity

as described previously. As a hypothalamic hormone, activated by stressful stimuli and threat appraisal, it releases corticotropin (ACTH) from the pituitary gland which then promotes release of cortisol and other glucocorticoids from the adrenal cortex. Vietnam veterans with PTSD have been shown to have elevated resting levels of cerebrospinal fluid CRF (Baker et al., 1999; Bremner, Licinio, et al., 1997) and enhanced hypothalamic release of CRF (Yehuda, 2002). Specified research on cognitive deficits associated with CRF concentration has not been carried out. Preclinical studies with the CRF receptor antagonist, antalarmin, have demonstrated reductions in cerebrospinal fluid CRF, reduced stress-induced fearful behavior, and suppression of both adrenergic and HPA responses to stress (Habib et al., 2000). Given its key role in mobilizing the human stress response as well as its increased expression among PTSD patients, there is good reason to predict that CRF antagonists might have beneficial clinical effects on PTSD-related symptoms and cognitive deficits. Although CRF antagonists are currently utilized in animal research and under development by pharmaceutical companies, none are available for clinical use.

Glucocorticoids

Glucocorticoids, such as cortisol, appear to impair PFC functions (such as working memory and amygdala restraint) by enhancing catecholamine levels during activation of the stress response (Arnsten, 2000; Roozendaal, McReynolds, & McGaugh, 2004). Although excessive HPA system activity does appear to be associated with trauma exposure and PTSD, it is controversial how this may be manifested. On the one hand, it may be expressed by elevated cortisol levels, as has been found in some PTSD patients and in children exposed to sexual trauma. On the other hand, it may be expressed by reduced cortisol levels associated with supersensitivity of glucocorticoid receptors (De Bellis et al., 1994; Friedman et al., 2001; Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Lemieux & Coe, 1995; Rasmusson & Friedman, 2002; Rasmusson et al., 2001; Yehuda, 2002; Yehuda, Boisoneau, Lowy, & Giller, 1995).

From a cognitive perspective, it has been proposed that abnormal HPA activity may have neurotoxic effects through activation of excitatory amino acids resulting in calcium influx into susceptible neurons (McEwen et al., 1992; Sapolsky, 2000). From a PTSD perspective, the theory that acute (or chronic) cortisol elevation and/or glucocorticoid receptor supersensitivity is neurotoxic has been invoked to explain reduced corpus callosum and intracranial volumes observed among traumatized children (De Bellis et al., 2002) and reduced hippocampal volumes among adults with PTSD (Bremner, Randall, et al., 1997; Bremner et al., 2003; Yehuda, 1999). In the only study that systematically explored the association between reduced hippocampal volume and cognitive impairment among PTSD patients, Vermetten

and associates (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003) observed decrements in verbal declarative memory that improved after an increase in hippocampal volume following antidepressant treatment (see later in the chapter). Since decrements in corpus callosum, hippocampus, or overall intracranial volume would be expected to have serious adverse effects on many key cognitive operations, it is important to explore the glucocorticoid neurotoxic hypothesis with the following caveat: it remains an open question whether such structural abnormalities precede the onset of PTSD or whether such reductions in brain nuclei develop after the occurrence of PTSD. Twin studies with war-zone-exposed Vietnam veterans and their nontraumatized monozygotic brothers indicate that both sets of twins have reduced hippocampal volume (Gilbertson et al., 2002). In addition, ongoing prospective studies with traumatized Israelis who developed PTSD have, as yet, failed to detect decrements in hippocampal volume associated with PTSD onset (Bonne et al., 2001). Taken together, those two studies suggest that reduced volumes of brain structures constitute a risk factor for PTSD but do not represent a serious consequence of this disorder.

Such considerations notwithstanding, it is useful to consider pharmacological strategies that might either prevent or ameliorate PTSD-related neurotoxic effects mediated by excessive HPA activity. With regard to early inter vention, potential treatments might include CRF antagonists or NPY enhancers, which would reduce the intensity of the acute stress response (Friedman, 2002). If the problem is excessive cortisol levels, a medication that inhibits cortisol synthesis (such as ketoconazole) or that blocks glucocorticoid receptors (such as mifepristone, RU-486) might be considered. If the problem is reduced cortisol and supersensitive glucocorticoid receptors, the opposite approach might be indicated in which glucocorticoids would be administered to downregulate supersensitive glucocorticoid receptors. Indeed, it has been shown that acute *hydrocortisone* treatment for septic shock effectively prevents the later development of PTSD (Schelling et al., 2001).

We will return to prevention of neurotoxicity later in this discussion when we consider glutamate antagonists, such as lamotrigine, which by inhibiting the release of excitatory amino acids, protect neurons by preventing toxic calcium influx. We will also consider treatments that promote neurogenesis and that have been shown to increase hippocampal volume in PTSD patients when we consider selective serotonin reuptake inhibitors (SSRIs) and other antidepressant medications.

THE GLUTAMATE AND GAMMA-AMINOBUTYRIC ACID SYSTEMS AND ANTICONVULSANT MEDICATIONS

Glutamate is the major excitatory, while gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain. Monoamines (such

as norepinephrine, serotonin, and dopamine) have received the most attention in the past because effective clinical agents (such as antidepressants and antipsychotic medications) are known to alter monoaminergic function. An important shift in focus has began to occur because our growing understanding of glutamatergic and GABAergic mechanisms indicates their crucial function in mediating most cognitive operations, their importance in the human stress response, and their probable role in the pathophysiology of PTSD. Anticonvulsant agents, also known as mood stabilizers, exert their primary actions on glutamate and/or GABA activity. Such actions also have potential importance in ameliorating cognitive deficits associated with PTSD.

Glutamate

There are two families of glutamate receptors: inotropic, which exert their actions through neuronal receptor ion channels, and metabotropic, which act by coupling with receptor-bound G proteins. There are three types of inotropic glutamate receptors named after the agonists to which they are differentially sensitive: *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxyazolepropionic acid (AMPA), and kainate. We focus on inotropic receptors in the following discussion. There are also three types of metabotropic receptors (M Glu I, II, and III), which act on intracellular messenger systems. Metabotropic receptors, through modulation of glutamate, GABA, and serotonin appear to mediate anxiolytic and antipsychotic actions (Zarate, Quirox, Payne, & Manji, 2002).

During the fear response NMDA receptors in the amygdala activate the fear circuit described previously. NMDA antagonists such as certain anticonvulsants inhibit such actions (Berlant, 2003; Davis & Whalen, 2001; Paul, Nowak, Layer, Popik, & Skolnick, 1994). In addition to enhancing the startle response and anxious behavior, AMPA receptors mediate long-term potentiation, sensitization, and kindling of brain neurons, which is an important neurobiological model of PTSD (Post, Weiss, & Smith, 1995; Post, Weiss, Li, Leverich, & Pert, 1999; Walker & Davis, 2002). Kainate receptors appear to promote fear and anxiety through actions in the periaqueductal gray and frontal cortex where they promote reduction of benzodiazepine (e.g., GABAergic) sites.

NMDA receptors are of great importance in cognition. They are crucial for all forms of learning, including fear conditioning (Bardgett et al., 2003; Liang, Hon, & Davis, 1994; Nakazawa et al., 2002) and extinction (Davis, 2002; Falls, Miserendino, & Davis, 1992; van der Meulen, Bilbija, Joosten, de Bruin, & Feenstra, 2003). They also play a major role in neurogenesis, the production of new neurons (Gould, McEwen, Tanapat, Galea, & Fuchs, 1997; Nacher, Alonso-Llosa, Rosell, & McEwen, 2003; Okuyama, Takagi, Kawai, Miyake-Takagi, & Takeo, 2004). AMPA recep-

tors may also promote neurogenesis through activation of brain-derived neurotropic factor (BDNF) (Mackowiak, O'Neill, Hicks, Bleakman, & Skolnick, 2002). An important model of dissociation involves the interplay of NMDA and AMPA receptors. Based on the observation that low doses of NMDA receptor antagonists such as ketamine or phencyclidine can produce alterations in thought content and processes such as paranoia, loosening of associations, tangentiality, and ideas of reference, while higher doses can produce dissociative symptoms such as slowed time perception (regarding the intensity, shape and color of objects), alterations in body perceptions, and derealization. The proposed model is that NMDA blockade intensifies glutamate stimulation of AMPA receptors (Chambers et al., 1999; Krystal, Bennett, Bremner, Southwick, & Charney, 1995). It is noteworthy that the dissociative effects of ketamine are blocked by lamotrigine, an anticonvulsant that inhibits glutamate release (Anand et al., 2000).

D-Cycloserine is a partial NMDA receptor agonist that has positive effects on memory deficits in animals (Monahan, Handelman, Hood, & Cordi, 1989; Thompson, Moskal, & Disterhoft, 1992), in elderly volunteers (Jones, Wesnes, & Kirby, 1991) and in Alzheimer's disease patients (Schwartz, Hashtroudi, Herting, Schwartz, & Deutsch, 1996). In a 12-week double-blind, placebo-controlled crossover design, PTSD patients currently treated with other medications were randomized to augmentation treatment with either D-cycloserine or placebo. Significant reductions in PTSD and anxiety (but not depression) symptom severity were observed. Furthermore, D-cycloserine treatment was associated with significant improvement in Wisconsin Card Sort perseverative error scores and near significant improvement in delayed recall on the Auditory Verbal Learning Test (Heresco-Levy et al., 2002).

Thus, the centrality of glutamatergic actions in cognitive deficits associated with PTSD has strong support both theoretically and from laboratory research. Such deficits include stress-induced problems with information processing, working memory, declarative memory, and dissociation.

Gamma-Aminobutyric Acid and Benzodiazepine Medication

GABA is the brain's major inhibitory neurotransmitter that suppresses stress-induced actions of the amygdala. GABA receptors within the basolateral amygdala inhibit glutamatergic excitation. Furthermore, serotonin enhances this GABAergic suppression of the amygdala (Berlant, 2003; Stutzmann & LeDoux, 1999), which is a major mechanism through which serotoninergic agents ameliorate both the acute stress response and PTSD symptomatology.

PTSD patients exhibit both reduced GABA plasma levels (Vaiva, Thomas, Ducroq, Fontaine, Boss, Devos, Rascle, et al., 2004) and reduced benzodiazepine receptor activity in the amygdala, PFC, and other brain ar-

eas (Bremner et al., 2000). Because benzodiazepine receptors are a part of the $GABA_A$ receptor complex, these findings suggest that deficiencies in GABAergic mechanisms in the amygdala, PFC, and elsewhere result in insufficient protection against the activating effects of norepinephrine and glutamate. It is possible that intrusive recollections, hyperarousal symptoms, and disinhibited social and emotional behavior observed among PTSD patients may be due to such deficient GABAergic function (Morgan, Krystal, & Southwick, 2003). It should be noted in this regard that pretreating animals later exposed to inescapable shock with benzodiazepines blocks stress-induced increases in norepinephrine in the amygdala, cortex, locus coeruleus, hypothalamus, and hippocampus (Drugan, Ryan, Minor, & Maier, 1984; Grant, Huang, & Redmond, 1980).

With regard to cognition, there is probably a therapeutic window within which enhancement of GABAergic activity will block the adverse cognitive effects of excessive norepinephrine and glutamate activity associated with acute stress, PTSD, and dissociative states. Excessive GABAergic activity, however, can impair cognitive function through dulling of the sensorium and suppression of cortical activity.

Given the above discussion, one might expect that treatment with benzodiazepines might ameliorate PTSD symptoms. Unfortunately, this has not been the case. A randomized clinical trial with *alprazolam* did not reduce core reexperiencing or avoidant/numbing symptoms, although it did lead to improvement in insomnia and generalized anxiety (Braun, Greenberg, Dasberg, & Lerer, 1990). Treatment of recently traumatized emergency room patients with *clonazepam* (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996) or the hypnotic benzodiazepine, *temazepam* (Mellman, Bustamante, David, & Fins, 2002) did not prevent the later development of PTSD. Other open trials with benzodiazepines have also been unsuccessful (Friedman, Davidson, Mellman, & Southwick, 2000).

Benzodiazepines act at $GABA_A$ receptors. *Baclofen* is a medication that activates $GABA_B$ receptors. Previous studies have shown that $GABA_B$ agonists have been effective in treating mood and anxiety disorders (Breslow et al., 1989; Krupitsky et al., 1993). An open-label study with baclofen was carried out, in which 9 of 11 veterans with PTSD experienced improvement in overall PTSD symptom severity, although there was no improvement in reexperiencing symptoms (Drake et al., 2003). As usual, specific tests of cognitive function were not included in this protocol. It does appear, however, that further trials with baclofen are warranted.

Anticonvulsant/Antikindling Agents

Anticonvulsant agents have been sporadically tested in small single-site studies for almost 20 years. Only one small, randomized clinical trial has

been carried out. Interest in this class of medications was initially prompted by their antikindling actions, since there has been great interest in sensitization/kindling hypotheses for a long time (Friedman, 1994; Post et al., 1995, 1999). More recently, appreciation of glutamatergic and GABAergic actions of anticonvulsants as well as detection of abnormalities in these two systems among PTSD patients has raised the level of interest in this class of medications. Finally, the development of several new anticonvulsant/mood stabilizers in recent years has motivated the pharmaceutical industry to support clinical trials utilizing these agents with PTSD patients.

What follows is a brief description of each anticonvulsant tested with PTSD patients, its mechanism of action, and the result of clinical trials. At the outset, it is important to recognize that all anticonvulsants may produce neurological symptoms and cognitive impairment as a side effect. Such side effects may include impaired concentration, memory problems, sedation, and confusion. Therefore, when treating PTSD, one must always weigh the relative risk of such side effects against the benefit of PTSD symptom reduction and improved cognition.

Carbamazepine

Carbamazepine is an antikindling agent thought to act by blocking sodium channels. Its antikindling effect suggests action at AMPA receptors. Chronic carbamazepine treatment has also been shown to elevate GABA concentrations in certain brain regions. There is also evidence that it antagonizes noradrenergic arousal (Berlant, 2003; Iancu, Rosen, & Moshe, 2002). Three open-label studies with veterans and adolescents observed improvement in PTSD symptom severity, impulse control, anger, and violent behavior (Lipper et al., 1986; Looff, Grimley, Kuller, Martin, & Shonfield, 1995; Wolfe, Alavi, & Mosnaim, 1988). A large retrospective study with military personnel indicated the effectiveness of carbamazepine in PTSD (Viola et al., 1997). Case reports with carbamazepine (Steward & Bartucci, 1986) and its close relative, oxcarbamazepine (Berigan, 2002a) have also been positive.

Valproate

Valproate is an antikindling agent that increases brain GABA levels, enhances GABA receptor sensitivity, and may suppress NMDA receptors (Berlant, 2003; Iancu et al., 2002). Four open-label trials and two case reports indicate the effectiveness of valproate for PTSD (Berigan & Holzgang, 1995; Clark, Canive, Calais, Qualls, & Tuason, 1999; Fesler, 1991; Goldberg, Cloitre, Whiteside, & Han, 2003; Petty et al., 2002; Szymanski & Olympia, 1991).

Lamotrigine

Lamotrigine inhibits glutamate release, blocks voltage-dependent sodium channels, antagonizes calcium channels, may block serotonin ($5\text{-}HT_2$) receptors, and may potentiate dopaminergic transmission (Goa, Ross, & Chrisp, 1993; Xie & Hagan, 1998). The only study on lamotrigine in PTSD is the only randomized clinical trial with any anticonvulsant. This was a 10-week trial in which 10 patients were randomized to lamotrigine and 5 to placebo monotherapy. Although the investigators reported amelioration of PTSD in 50% (5/10) of lamotrigine patients in contrast to 25% (1/4) placebo patients (Hertzberg et al., 1999), their interpretation has been challenged (Berlant, 2003) based on a reanalysis of these data. Given the low statistical power due to the small sample size, further studies with lamotrigine are certainly warranted, given its unique pharmacological profile.

Topirimate

Topirimate is an extremely interesting anticonvulsant that suppresses glutamate function while enhancing GABAergic activity (Chengappa, John, & Parepally, 2002). It has antikindling actions as well, probably through AMPA blockade (Zullino, Krenz, & Besson, 2003). From a theoretical perspective, it seems like an excellent medication for PTSD patients. From a clinical perspective, it is one of the few psychotropic medications available that promotes weight loss rather than weight gain (Van Ameringen, Mancini, Pipe, Campbell, & Oakman, 2002). An open-label trial with 35 PTSD patients focused exclusively on reexperiencing symptoms such as nightmares, intrusive recollections, and flashbacks. Overall, 71% patients had complete remission of those symptoms and 21% reported a partial response (Berlant & van Kammen, 2002). Further trials are warranted in which the full spectrum of PTSD symptoms as well as cognitive function are monitored.

Gabapentin

Gabapentin appears to increase GABA turnover in certain brain regions (Berlant, 2003). Evidence regarding its efficacy in PTSD is sparse. Three case reports describe amelioration of PTSD symptoms (Berigan, 2002b; Brannon, Labbate, & Huber, 2000; Malek-Ahmadi, 2003). The most extensive report is a retrospective chart review of 30 patients, most of whom (90%) received another medication in addition to gabapentin. Since dropout rates and adverse side effects (especially excessive daytime sedation) were significant (Hamner, Brodrick, & Labbate, 2001), further research is clearly needed.

Tiagabine

Tiagabine is an antikindling agent that inhibits glial GABA reuptake, thereby increasing GABA concentration at both GABA-A and GABA-B receptors. Three case reports describe its effectiveness in PTSD (Berigan, 2002c; Schwartz, 2002; Taylor, 2003).

Vigabatrin

Vigabatrin increases GABA levels through inhibition of GABA transaminase (Berlant, 2003). A report on five cases of PTSD treated with this agent emphasized its reduction of the startle response along with improvement in anxiety and insomnia (Macleod, 1996).

To summarize, anticonvulsant agents have diverse actions on glutamate, GABA, and other neurotransmitters. Findings are generally favorable regarding amelioration of PTSD symptoms but all but one of these reports are either open-label trials or case reports. The single randomized trial (with lamotrigine) included only 15 patients and lacked sufficient statistical power. Cognitive performance was not assessed formally in any of these trials, so it is impossible to determine whether reduction in PTSD symptoms was reliably associated with improved information processing or memory function. Finally, these are not benign medications and their clinical utilizations may produce adverse side effects regarding cognitive operations.

THE SEROTONIN SYSTEM AND ANTIDEPRESSANT MEDICATIONS

The Serotonin System

The serotonergic system has important interactions with the adrenergic, HPA, glutamate, GABA, and dopamine systems. Most serotonin neurons have their origin in two midbrain loci, the dorsal and median raphe nuclei, respectively, which have extensive connections with key limbic structures mediating stressful or threatening stimuli. Excessive stress, HPA activity, or PTSD produces downregulation of anxiolytic, 5-HT_{1A} and upregulation of anxiogenic, 5-HT_{2A} receptors.

There also appear to be synergistic interactions between 5-HT_{1A} and GABA receptors with regard to acute stress and PTSD. It is thought that stimulation of 5-HT_{1A} receptors in the amygdala potentiates GABA neurons which, in turn, antagonize the excitatory glutamate neurotransmission that mediates stress-related amygdala activation (Charney, 2004; Vermetten & Bremner, 2002). This model suggests three potential amygdala-based target sites for pharmacological intervention: antagonism of glutamate, potentiation of GABA, and enhancement of serotonin neurotransmission.

As with NMDA receptors, serotonin 5-HT_{1A} receptors also promote neurogenesis in the hippocampus. It has been shown that selective serotonin reuptake inhibitors (SSRIs), as well as all clinically effective antidepressants promote neurogenesis through activation of BDNF and cyclic adenosine monophosphate (cAMP) (Duman, Nakagawa, & Malberg, 2001). This obviously has important implications for cognitive function, as discussed previously with regard to the reduced hippocampal volume of brain structures observed among PTSD patients.

Clinical studies have long indicated that many symptoms observed among PTSD patients are associated with serotonin deficiency such as impulsivity, suicidal behavior, rage, aggression, depression, panic, obsessional thoughts, and chemical dependency (Friedman, 1990). Furthermore, since the serotoninergic agonist M-chorophenylpiperazine (mCPP) can provoke panic reactions and dissociative flashbacks in PTSD but not control subjects (Southwick et al., 1997), there is reason to presume that serotonin 5-HT-2 antagonists might be clinically useful in this regard.

Selective Serotonin Reuptake Inhibitors

SSRIs are the treatment of choice for PTSD patients as attested by three independent clinical practice guidelines (American Psychiatric Association, in press; Friedman et al., 2000; VA/DoD, 2004). The only two medications to receive approval as indicated treatments for PTSD by the U.S. Food and Drug Administration are the SSRIs, sertraline and paroxetine. Multisite randomized clinical trials with *sertraline* (Brady et al., 2000; Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001) and *paroxetine* (Marshall, Beebe, Oldham, & Zaninelli, 2001; Tucker et al., 2001) demonstrated that both agents significantly reduced PTSD symptoms in contrast to placebo. It was also shown that if sertraline treatment was extended from 12 to 36 weeks that 55% of nonresponding patients would convert to medication responders (Lonborg et al., 2001). Finally, discontinuation of SSRI treatment is associated with clinical relapse and a return of PTSD symptoms (Davidson, Pearlstein, et al., 2001; Martenyi, Brown, Zhang, Koke, & Prakash, 2002; Rapaport, Endicott, & Clary, 2002). Randomized clinical trials with *fluoxetine* (Martenyi, Brown, Zhang, Prakash, & Koke, 2002; van der Kolk et al., 1994) and open-label studies with *fluvoxamine* (De Boer, Op den Velde, Falger, Hovens, De Groen, & Van Duijn, 1992; Escalona, Canive, Calais, & Davidson, 2002; Marmar, Schoenfeld, Weiss, Metzler, Zatzick, Wu, et al., 1996) and *citalopram* (Seedat, Lockhat, Kaminer, Zungu-Dirwayi, & Stein, 2001) indicate that these SSRIs are also effective agents. As with other medications discussed previously, most research has focused on reduction of PTSD symptoms with one notable exception (see later discussion). Since SSRIs have a broad spectrum of action

and are effective for PTSD reexperiencing, avoidance/numbing, and hyperarousal symptoms, they have a general positive impact on cognition by improving concentration and attenuating the distraction of intrusive recollections. Furthermore, within the amygdala, inhibition of glutamatergic excitation through serotonergic potentiation of GABAergic activity would be expected to have the beneficial cognitive effects produced by any intervention that reduces stress-induced amygdala activation.

A very exciting recent study with the SSRI paroxetine addresses two important questions regarding cognitive deficits among PTSD patients: declarative memory and hippocampal volume. Vermetten and associates (2003) assessed declarative memory and hippocampal volume among 20 PTSD patients who completed 9–12 months of treatment with paroxetine. These investigators observed a significant improvement in Wechsler Memory Scale—Revised performance after treatment in the following domains: logical memory (delayed recall and percent retention) and figural memory (immediate recall). Significant improvement was also observed with the Selective Reminding Test in verbal memory (total recall, long-term storage, long-term retrieval, continuous long-term retrieval, and delayed recall) as well as in visual memory (total recall, long-term storage, long-term retrieval, and continuous long-term retrieval). Most remarkably, these investigators also observed a 4.6% increase in mean hippocampal volume as measured by magnetic resonance imaging (MRI).

Other Serotonergic Antidepressants

Nefazadone and *trazodone* are two antidepressants that enhance serotonergic activity through a dual mechanism that combines an SSRI action with postsynaptic, 5-HT_2 blockade. As with most other medications reviewed, there are no published studies in which cognitive function was monitored in conjunction with treatment. Trials with nefazadone have been much more promising, including a randomized ttial in which treatment with nefazadone was as effective as sertraline (Saygin, Sungur, Sabol, & Cetinkaya, 2002). Similar positive results have been obtained in open-label nefazadone trials (Davis, Nugent, Murray, Kramer, & Petty, 2000; Hertzberg, Feldman, Beckham, Moore, & Davidson, 1998; Hidalgo et al., 1999). Despite these promising results, nefazadone has been recently withdrawn from the American market because of liver toxicity. The reason for including nefazadone in this review is to demonstrate the utility of non-SSRI medications that enhance serotonergic actions among PTSD patients.

Trazodone has limited efficacy in monotherapy for PTSD. Due to its sedating effects and serotoninergic action, it is often used in conjunction with SSRIs to counter medication-induced insomnia (Friedman et al., 2000).

OTHER ANTIDEPRESSANTS

Although SSRIs are the current first-line medications for PTSD, it is useful to consider other effective antidepressants whose action is not restricted to the serotonergic system. These include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and newer agents such as mirtazapine, venlafaxine, and bupropion.

Tricyclic Antidepressants

These medications block presynaptic reuptake of both serotonin and norepinephrine. Some TCAs exert their actions primarily on serotonin reuptake (e.g., amitriptyline), others primarily on norepinephrine reuptake (e.g., desipramine), and some on both neurotransmitter systems (e.g., imipramine). From the previous discussion, it is clear why serotonin enhancement might be beneficial for PTSD patients. Blockade of adrenergic reuptake (which is also effective for panic disorder) probably exerts its therapeutic action either through enhancement of (presynaptic inhibitory) alpha$_2$ receptors and/or through downregulation of postsynaptic beta receptors. In either case, the end result is a reduction in adrenergic activity in the amygdala, PFC, and locus coeruleus. Randomized clinical trials with *imipramine* (Kosten, Frank, Dan, McDougle, & Giller, 1991) and *amitryptyline* (Davidson et al., 1990) but not *desipramine* (Reist et al., 1989) have demonstrated symptom reduction in PTSD patients.

One consequence of the effectiveness and benign side effect profiles of SSRIs and newer antidepressants has been a loss of investigator interest in older but still effective agents such as TCAs and MAOIs. A remarkable exception to this is a prospective study comparing imipramine with the hypnotic, chloral hydrate, among pediatric burn patients in which imipramine treatment was effective in treating young burn victims with acute stress disorder (Robert, Blakeney, Villarreal, Rosenberg, & Meyer, 1999).

Monoamine Oxidase Inhibitors

MAOIs block the intraneuronal metabolic breakdown of serotonin, norepinephrine, dopamine, and other monoamines. By preventing enzymatic destruction of these neurotransmitters, more is available for presynaptic release. Thus, their therapeutic action may result from downregulation of postsynaptic receptors and, possibly, by downregulating adrenergic activity in the locus coeruleus (Davidson, Walker, & Kilts, 1987). A randomized clinical trial with the MAOI, *phenelzine*, with Vietnam combat veterans was extremely successful in reducing reexperiencing and arousal PTSD symptoms (Kosten et al, 1991). Results have been mixed in open-label trials

(Davidson et al., 1987; Lerer, Ebstein, Shestatzky, Shemesh, & Greenberg, 1987; Milanes, Mack, Dennison, & Slater, 1984), and a small, methodologically flawed 5-week crossover study had negative results (Shestatzky, Greenberg, & Lerer, 1988). Finally, an open trial with the reversible MAO-A inhibitor, moclobemide (Neal, Shapland, & Fox, 1997) reported improvement in all three PTSD symptom clusters. Again, no formal testing of cognitive function was carried out in any of these investigations.

Newer Antidepressants

Mirtazepine

Mirtazepine has both serotonergic actions (blockade of postsynaptic 5-HT_2 and 5-HT_3 receptors) as well as action at presynaptic alpha$_2$-adrenergic receptors. In one randomized trial (versus placebo) (Davidson et al., 2003) and one open-label 8-week trial in Korea (Bahk et al., 2002), mirtazepine effectively reduced PTSD symptom severity. An interesting case report describes the usefulness of mirtazepine for traumatic nightmares (or for postawaking memory of such nightmares) among 300 refuges who had previously failed to benefit in this regard from other medications (Lewis, 2002).

Venlafaxine

Venlafaxine blocks presynaptic reuptake of norepinephrine and serotonin. It also has a much less potent effect on blocking dopamine reuptake. Although there have been promising reports, it has not been tested adequately as a treatment for PTSD (Hamner & Frueh, 1998).

Bupropion

Bupropion blocks presynaptic reuptake of norepinephrine and dopamine, but not serotonin. Anecdotal evidence and open trials suggests that it may be effective in PTSD (Canive, Clark, Calais, Qualls, & Tuason, 1998).

THE DOPAMINERGIC SYSTEM AND ANTIPSYCHOTIC MEDICATIONS

Dopamine

During uncontrollable stress, amygdala activation produces PFC dopamine release (Charney, 2004). There is evidence that dopamine D_1 receptor agonists can produce stress-induced PFC impairments in working memory (Zahrt, Taylor, Mathew, & Arnsten, 1997) and that both D_1 and D_2 recep-

tor antagonists can prevent such cognitive deficits (Arnsten, 2000; Druzin, Kurzina, Malinina, & Kozlov, 2000).

Excessive dopamine release may have a role in PTSD hyperarousal, hypervigilence, and possibly in provoking the brief paranoid/psychotic states sometimes observed among PTSD patients. It is surprising how little PTSD research has focused on dopamine in comparison with neurotransmitters discussed previously. Elevated urinary and plasma dopamine concentrations have been found among PTSD subjects (Hamner & Diamond, 1993; Lemieux & Coe, 1995; Yehuda et al., 1994).

There is one report that the D2A1 dopamine receptor allele increases the risk for PTSD (Comings, Muhleman, & Gysin, 1996). It is interesting, in this regard, that PTSD patients with the D2A1 allele show more improvement in social functioning (but not depression or anxiety) following paroxetine treatment, in contrast to the PTSD patients who do not posses the D2A1 allele. Thus, the bad news is that this allele may increase risk of developing PTSD, but among those affected with this disorder, the D2A1 allele may be prognostic for better responsivity to SSRI treatment in social function, but not clinical symptoms.

Atypical Antipsychotic Medications

There is a small but growing literature on favorable results with atypical antipsychotic agents. This contrasts with a general consensus that conventional antipsychotic agents (e.g., chlorpromazine or haloperidol) have no place in PTSD treatment because of a very unfavorable risk–benefit ratio due to questionable clinical usefulness plus serious side effects, especially tardive dysknesia (Friedman et al., 2000). One the other hand, atypical antipsychotics have two actions, D_2 receptor blockade (which they share with conventional antipsychotics) and a unique 5-HT_2 receptor antagonism. As a result, they not only have a much more benign side effect profile (e.g., rare extrapyramial complications), but also unique therapeutic actions, such as efficacy against negative symptoms of schizophrenia. In PTSD treatment, atypicals have usually been utilized as adjunctive agents for refractory patients who have failed to respond to SSRIs or other antidepressants. Although there is little empirical evidence to guide general practice, these medications are usually prescribed to ameliorate dissociation, hypervigilance/paranoia, psychosis, hyperarousal, irritability, and aggression. There have not been any systematic attempts to asses enhancement of cognition among PTSD patients treated with atypical antipsychotics. As with the vast majority of medications discussed in this review, the focus has been on symptom reduction with the implication that amelioration of intrusive recollections, dissociative, psychogenic amnesia, and global cogni-

tive problems indicates the potential utility of those medications for improving more specific cognitive operations.

There are published reports on three antipsychotic medications: risperidone, quetiapine and olanzapine. Results from a randomized trial (Hamner, Faldowski, et al., 2003), an open-label trial (Monnelly, Ciraulo, Knapp, & Keane, 2003), and several case reports with *risperidone* as adjunctive therapy suggest that it reduces overall PTSD symptom severity in addition to reducing dissociative flashbacks and aggressive behavior. Similar findings have been obtained with *quetiapine* as an adjunctive agent in which an open-label trial (Hamner, Deitsch, Brodrick, Ulmer, & Lorberbaum, 2003), a retrospective client review (Sokolski, Densen, Lee, & Reist, 2003), and several case reports indicate beneficial effects in reducing PTSD symptoms among refractory patients who had failed to respond to SSRIs and other medications. Finally, a randomized trial with *olanzapine* (Stein, Kline, & Matloff, 2002) also indicated its effectiveness as an adjunctive agent in reducing PTSD symptoms among chronic patients who had failed to respond to other agents.

To summarize, what little research has been conducted on dopamine mechanisms in PTSD patients suggests that dopamine blockade might be a beneficial approach. Small open-label and randomized trials with atypical antipsychotics as adjunctive agents for nonrespondant chronic PTSD patients have been encouraging. Little more than PTSD symptom severity has been monitored in these trials but there are indications that successful treatment enhances PFC function in general and improves cognition with respect to working memory, information processing, dissociation, hypervigilance/paranoia, and psychotic symptoms.

SUMMARY

It is clear that PTSD is associated with impairments in cognitive function. Our growing understanding of the underlying pathophysiology of this disorder has gradually narrowed this focus to alterations in information processing, working memory, declarative memory, dissociation, and related symptoms. Neuropharmacological mechanisms associated with altered amygdala, hippocampal, and prefrontal cortex function include abnormal adrenergic, HPA, glutamatergic, GABAergic, serotonergic, and dopaminergic function. There are, potentially, a number of pharmacological interventions that might improve PTSD-related cognitive disruption while ameliorating clinical symptoms. With the exception of one study regarding the SSRI, paroxetine (Vermetten et al., 2003), this possibility has not been addressed systematically in clinical research. Hopefully, this important area will begin to receive the attention it deserves.

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